PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 April 2000 (25.04.00)	
International application No. PCT/US99/18771	**Applicant's or agent's file reference** 3260.84-304
International filing date (day/month/year) 20 August 1999 (20.08.99)	**Priority date** (day/month/year) 21 August 1998 (21.08.98)
Applicant SIMS, John, E. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 March 2000 (20.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, *chemin des Colombettes*** **1211 Geneva 20, Switzerland**	Authorized officer R. Forax
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED

PCT DEC 04 2000

FINNEGAN, HENDERSON, FARABOW, GARRETT AND DUNNER, LLP

To:

GARRETT, Arthur S.
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23.11.2000

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
3260.84-304	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/18771	20/08/1999	21/08/1998

Applicant
IMMUNEX CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Danissen, P Tel.+49 89 2399-8862

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
3260.84-304		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/18771	20/08/1999	21/08/1998

International Patent Classification (IPC) or national classification and IPC
C12N15/25

Applicant
IMMUNEX CORPORATION et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/03/2000	23.11.2000

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Steffen, P

Telephone No. +49 89 2399 7307

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/18771

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-50	as originally filed

Claims, No.:

1-20	as originally filed

Drawings, sheets:

1/4-4/4	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 17-20 (I.A.).

because:

☒ the said international application, or the said claims Nos. 17-20 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 8-11,15,16

	No:	Claims	1-7,12-14,17-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 17.08.2000 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

Independent claims 1-3, parts (b) and (c), 12 and 13.

No basis could be found in the application as originally filed for a polynucleotide encoding a **fragment of a polypeptide** selected from either SEQ ID NO 8 or 13, and **with the specific properties** of being able to activate phosphorylation of IKBα or p38MAP kinase or to increase cell surface expression of ICAM-1 (claims 1-3, parts (b)). Similarly no basis is found for a polynucleotide that encodes a polypeptide having **at least 80% identity** with SEQ ID NO 8 or 13 and **with the specific properties** of being able to activate phosphorylation of IKBα or p38MAP kinase or to increase cell surface expression of ICAM-1 (claims 1-3 (parts (c)). Moreover no basis could be found in the application as originally filed for an isolated polypeptide being 80 % identical to the polypeptides of SEQ ID NO 6, 8 or 13 and having the ability to activate phosphorylation of IKBα or p38MAP kinase or a fragment which has the ability to increase cell surface expression of ICAM-1 (claim 12). Please refer in this context also to the passages of the description, page 21, lines 15-21 and page 25, lines 24-28. Analogously no basis could be found for a soluble fragment of a polypeptide of SEQ ID NO 6, 8 or 13 with the above mentioned biological properties (claim 13).

Due to the above enumerated unallowed amendments concerning claims 1-3, 12 and 13 and due to the fact that new claims 6-8 and 14-16 are dependent on claims 1-3, the present report is based on claims 1-20 as originally filed and the newly filed claims with the letter dated 17.08.2000 do not form part of the basis of the present report.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 17-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: M. MARRA ET AL: 'The washU-HHMI Mouse EST project' EMBL DATABASE ENTRY MMA30324, ACCESSION NUMBER AA030324, 21 January 1997 (1997-01-21).

D2: EP-A-0 855 404 (SMITHKLINE BEECHAM CORP) 29 July 1998 (1998-07-29)

D3: C.A. DINARELLO: 'Interleukin-1' CYTOKINE & GROWTH FACTOR REVIEW, vol. 8, no. 4, December 1997 (1997-12), pages 253-265.

The present application refers to isolated nucleic acids (e.g. SEQ ID NO's 5, 7 and 12) encoding a further member of the interleukin-1 (IL-1) ligand family and the corresponding proteins (e.g. SEQ ID NO's 6, 8 and 13), termed IL-1 epsilon by the applicants. Claimed are also further embodiments of the respective nucleic acid and protein sequences.

The subject-matter of claims 8-11, 15 and 16 is not anticipated by a prior art document on file and is thus considered to comply with article 33(2) PCT.

The subject-matter of claims 1-7, 12-14 and 17-20 is not novel in view of article 33(2) PCT for the following reasons.

The isolated nucleic acid molecules of claim 1, in respect of the broad definitions given in points (c)-(f) (see also point VIII. of present communication), are anticipated by the teachings of D1 (EST sequence, 74.2 % identity with SEQ ID NO 5 in a 213 bp overlap, in particular also for species homolog) and D2 (page 14, SEQ ID NO 1, 70.9 % identity with SEQ ID NO 5 in a 203 bp overlap). Therefore novelty of claims 2 and 12 is also anticipated

by D1 and D2 (page 7). Since claim 1 encompasses the nucleic acid of SEQ ID NO 1 of D2, the polypeptide of claim 3 is anticipated by SEQ ID NO 2 of D2, page 15). In a similar manner, the subject-matter of claims 4-7, 13, 14, 17-20 (in view of the vague IL-1 epsilon definition, see also point VIII.) is therefore anticipated by the teachings of D2 (D2, page 9, line 46; page 7, lines 35-55; page 9, lines 13-34; page 7, line 35 to page 8, line 16; page 9 lines 38-45). For the antibodies of claims 6 and 7, it is noted in more general manner, that strong sequence identities in certain regions of the polypeptides of the application and the SEQ ID NO 6 (e.g. 63.2 % identity in 68 amino acid overlap) exist. Therefore the antibodies reactive to the SEQ ID NO 2 of D2 (D2, page 9) might always also be reactive with the polypeptide of SEQ IN NO 6 of the application and thus anticipate the subject-matter of claims 6 and 7.

In consequence, claims 1-7, 12-14 and 17-20 are not novel and not based on inventive activity in view of articles 33(2) and 33(3) PCT.

In a more general manner, claims 1-20 lack inventive activity, contrary to the requirements of article 33(3) PCT for the following reasons.

As mentioned above, the present application refers to isolated nucleic acids (e.g. SEQ ID NO's 5, 7 and 12) encoding a further member of the interleukin-1 (IL-1) ligand family and the corresponding proteins (e.g. SEQ ID NO's 6, 8 and 13), termed IL-1 epsilon by the applicants. D1 discloses an EST sequence with no known function. D3 discloses several members of the IL-1 ligand family and D2 discloses and additional one. The skilled person, wishing to find novel members of the IL-1 ligand family (see present application, page 3, lines 3-4) would therefore have been able to provide the further members of this family as taught by the present application, given the teachings of D1-D3, in an obvious manner and with a reasonable expectation of success as set forth below. By searching the databases with routine knowledge and known computer programs using either single sequence information or homology regions of the existing members of the IL-1 ligand family, the skilled person would have naturally come across the database entry of D1 and classified this murine sequence to the members of the IL-1 ligand family. Subsequently he could have reasonably expected, that because this ligand is present in mice, that this molecule also exists in humans and used the cDNA clone for a subsequent probe in routine cloning of the human ortholog thereof. Therefore the isolated nucleic acids of claim 1 are not based on inventive activity. Since all further claims refer to further obvious embodiments

of claim 1, they are also not based on inventive activity.

In conclusion, claims 1-20 lack invective activity, contrary to the requirements of article 33(3) PCT.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10):

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
D4: WO98/47921	29.10.1998	17.04.1998	06.08.1998

Examination of the present application was carried out under the presumption of a valid priority. Under rule 70.10, D4 is to be considered relevant for the questions of novelty and of inventive activity for claims 1-20.

Re Item VIII
Certain observations on the international application

The following objections relate to article 6 PCT.

Claim 1 displays the following clarity problems. Point (c) refers to isolated nucleic acids molecules that hybridise to a given sequence. Since these nucleic acids are not limited in any manner (e.g. biological functional restriction, length and homology restriction), it is not understood what exactly is encompassed by this part of the claim. Therefore, yet existing short oligonucleotides, with no biological relation to the sequences of the invention could also be encompassed by this claim. Point (d) refers to nucleic acids "derived by *in vitro* mutagenesis" from SEQ ID NO's 5, 7 and 12. In the absence of any restriction, it cannot be understood what the end product will be since the number of mutations is not limited and thus it is possible to change the whole sequences claimed. Point (e) is unclear with respect to "as a result of the genetic code". This can mean different things, like for example the degeneracy of the genetic code or the genetic code (e.g. the nucleotide sequence) of

another species. Finally the term IL-1 epsilon is an arbitrary term with no recognised meaning in the art. Therefore this term is not meaningful in the absence of sequence information. This latter remark also applies to claims 13, 17 and 18.

The following claims lack correct support by the description. Claim 6 with respect to "that binds" (the description only refers to "that **specifically** binds", page 42, line 22, for example). Claim 14 with respect to plant cells, which are not enumerated as possible host cells in the description.

Claim 13 is unclear because of a presumably wrong dependency (e.g. a host cell of claim 2, whereas claim 2 refers to a recombinant vector).

Claim 17 is completely unclear with the broad reference to "an antagonist". Here it is not understood what all these antagonists may be. They may be known or unknown molecules and they may be known molecules already used in inflammatory conditions. Therefore it is not clearly understood how the scope of this claim can be appreciated.

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PATENT COOPERATION **ATY**

REC'D 28 NOV 2000

PO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
3260.84-304		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/18771	20/08/1999	21/08/1998
International Patent Classification (IPC) or national classification and IPC		
C12N15/25		
Applicant		
IMMUNEX CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/03/2000	23.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Steffen, P Telephone No. +49 89 2399 7307

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/18771

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-50 as originally filed

Claims, No.:

1-20* as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 17-20 (I.A.).

because:

☒ the said international application, or the said claims Nos. 17-20 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 8-11,15,16

	No:	Claims	1-7,12-14,17-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 17.08.2000 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

Independent claims 1-3, parts (b) and (c), 12 and 13.

No basis could be found in the application as originally filed for a polynucleotide encoding a **fragment of a polypeptide** selected from either SEQ ID NO 8 or 13, and **with th specific properties** of being able to activate phosphorylation of IKBα or p38MAP kinase or to increase cell surface expression of ICAM-1 (claims 1-3, parts (b)). Similarly no basis is found for a polynucleotide that encodes a polypeptide having **at least 80% identity** with SEQ ID NO 8 or 13 and **with the specific properties** of being able to activate phosphorylation of IKBα or p38MAP kinase or to increase cell surface expression of ICAM-1 (claims 1-3 (parts (c)). Moreover no basis could be found in the application as originally filed for an isolated polypeptide being 80 % identical to the polypeptides of SEQ ID NO 6, 8 or 13 and having the ability to activate phosphorylation of IKBα or p38MAP kinase or a fragment which has the ability to increase cell surface expression of ICAM-1 (claim 12). Please refer in this context also to the passages of the description, page 21, lines 15-21 and page 25, lines 24-28. Analogously no basis could be found for a soluble fragment of a polypeptide of SEQ ID NO 6, 8 or 13 with the above mentioned biological properties (claim 13).

Due to the above enumerated unallowed amendments concerning claims 1-3, 12 and 13 and due to the fact that new claims 6-8 and 14-16 are dependent on claims 1-3, the present report is based on claims 1-20 as originally filed and the newly filed claims with the letter dated 17.08.2000 do not form part of the basis of the present report.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 17-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: M. MARRA ET AL: 'The washU-HHMI Mouse EST project' EMBL DATABASE ENTRY MMA30324, ACCESSION NUMBER AA030324, 21 January 1997 (1997-01-21).

D2: EP-A-0 855 404 (SMITHKLINE BEECHAM CORP) 29 July 1998 (1998-07-29)

D3: C.A. DINARELLO: 'Interleukin-1' CYTOKINE & GROWTH FACTOR REVIEW, vol. 8, no. 4, December 1997 (1997-12), pages 253-265.

The present application refers to isolated nucleic acids (e.g. SEQ ID NO's 5, 7 and 12) encoding a further member of the interleukin-1 (IL-1) ligand family and the corresponding proteins (e.g. SEQ ID NO's 6, 8 and 13), termed IL-1 epsilon by the applicants. Claimed are also further embodiments of the respective nucleic acid and protein sequences.

The subject-matter of claims 8-11, 15 and 16 is not anticipated by a prior art document on file and is thus considered to comply with article 33(2) PCT.

The subject-matter of claims 1-7, 12-14 and 17-20 is not novel in view of article 33(2) PCT for the following reasons.

The isolated nucleic acid molecules of claim 1, in respect of the broad definitions given in points (c)-(f) (see also point VIII. of present communication), are anticipated by the teachings of D1 (EST sequence, 74.2 % identity with SEQ ID NO 5 in a 213 bp overlap, in particular also for species homolog) and D2 (page 14, SEQ ID NO 1, 70.9 % identity with SEQ ID NO 5 in a 203 bp overlap). Therefore novelty of claims 2 and 12 is also anticipated

by D1 and D2 (page 7). Since claim 1 encompasses the nucleic acid of SEQ ID NO 1 of D2, the polypeptide of claim 3 is anticipated by SEQ ID NO 2 of D2, page 15). In a similar manner, the subject-matter of claims 4-7, 13, 14, 17-20 (in view of the vague IL-1 epsilon definition, see also point VIII.) is therefore anticipated by the teachings of D2 (D2, page 9, line 46; page 7, lines 35-55; page 9, lines 13-34; page 7, line 35 to page 8, line 16; page 9 lines 38-45). For the antibodies of claims 6 and 7, it is noted in more general manner, that strong sequence identities in certain regions of the polypeptides of the application and the SEQ ID NO 6 (e.g. 63.2 % identity in 68 amino acid overlap) exist. Therefore the antibodies reactive to the SEQ ID NO 2 of D2 (D2, page 9) might always also be reactive with the polypeptide of SEQ IN NO 6 of the application and thus anticipate the subject-matter of claims 6 and 7.

In consequence, claims 1-7, 12-14 and 17-20 are not novel and not based on inventive activity in view of articles 33(2) and 33(3) PCT.

In a more general manner, claims 1-20 lack inventive activity, contrary to the requirements of article 33(3) PCT for the following reasons.

As mentioned above, the present application refers to isolated nucleic acids (e.g. SEQ ID NO's 5, 7 and 12) encoding a further member of the interleukin-1 (IL-1) ligand family and the corresponding proteins (e.g. SEQ ID NO's 6, 8 and 13), termed IL-1 epsilon by the applicants. D1 discloses an EST sequence with no known function. D3 discloses several members of the IL-1 ligand family and D2 discloses and additional one. The skilled person, wishing to find novel members of the IL-1 ligand family (see present application, page 3, lines 3-4) would therefore have been able to provide the further members of this family as taught by the present application, given the teachings of D1-D3, in an obvious manner and with a reasonable expectation of success as set forth below. By searching the databases with routine knowledge and known computer programs using either single sequence information or homology regions of the existing members of the IL-1 ligand family, the skilled person would have naturally come across the database entry of D1 and classified this murine sequence to the members of the IL-1 ligand family. Subsequently he could have reasonably expected, that because this ligand is present in mice, that this molecule also exists in humans and used the cDNA clone for a subsequent probe in routine cloning of the human ortholog thereof. Therefore the isolated nucleic acids of claim 1 are not based on inventive activity. Since all further claims refer to further obvious embodiments

of claim 1, they are also not based on inventive activity.

In conclusion, claims 1-20 lack invective activity, contrary to the requirements of article 33(3) PCT.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10):

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
D4: WO98/47921	29.10.1998	17.04.1998	06.08.1998

Examination of the present application was carried out under the presumption of a valid priority. Under rule 70.10, D4 is to be considered relevant for the questions of novelty and of inventive activity for claims 1-20.

Re Item VIII
Certain observations on the international application

The following objections relate to article 6 PCT.

Claim 1 displays the following clarity problems. Point (c) refers to isolated nucleic acids molecules that hybridise to a given sequence. Since these nucleic acids are not limited in any manner (e.g. biological functional restriction, length and homology restriction), it is not understood what exactly is encompassed by this part of the claim. Therefore, yet existing short oligonucleotides, with no biological relation to the sequences of the invention could also be encompassed by this claim. Point (d) refers to nucleic acids "derived by *in vitro* mutagenesis" from SEQ ID NO's 5, 7 and 12. In the absence of any restriction, it cannot be understood what the end product will be since the number of mutations is not limited and thus it is possible to change the whole sequences claimed. Point (e) is unclear with respect to "as a result of the genetic code". This can mean different things, like for example the degeneracy of the genetic code or the genetic code (e.g. the nucleotide sequence) of

another species. Finally the term IL-1 epsilon is an arbitrary term with no recognised meaning in the art. Therefore this term is not meaningful in the absence of sequence information. This latter remark also applies to claims 13, 17 and 18.

The following claims lack correct support by the description. Claim 6 with respect to "that binds" (the description only refers to "that **specifically** binds", page 42, line 22, for example). Claim 14 with respect to plant cells, which are not enumerated as possible host cells in the description.

Claim 13 is unclear because of a presumably wrong dependency (e.g. a host cell of claim 2, whereas claim 2 refers to a recombinant vector).

Claim 17 is completely unclear with the broad reference to "an antagonist". Here it is not understood what all these antagonists may be. They may be known or unknown molecules and they may be known molecules already used in inflammatory conditions. Therefore it is not clearly understood how the scope of this claim can be appreciated.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/18771

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/25 C07K14/545 C07K16/24 A61K38/20 A61P29/00 A61P37/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. MARRA ET AL: "The washU-HHMI Mouse EST project" EMBL DATABASE ENTRY MMA30324, ACCESSION NUMBER AA030324, 21 January 1997 (1997-01-21), XP002125184 cited in the application & UNPUBLISHED,	1,2
X	EP 0 855 404 A (SMITHKLINE BEECHAM CORP) 29 July 1998 (1998-07-29) sequence ID no 1 page 18 claims	1-7
A	C.A. DINARELLO: "Interleukin-1" CYTOKINE & GROWTH FACTOR REVIEW , vol. 8, no. 4, December 1997 (1997-12), pages 253-265, XP002098883 the whole document	1-14, 17-20

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1999	11/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Le Cornec, N

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/18771

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 449 758 A (HARTLEY JAMES L) 12 September 1995 (1995-09-12) cited in the application the whole document	15,16
P,X	WO 98 47921 A (SCHERING CORP) 29 October 1998 (1998-10-29)	1-7, 12-14, 17,18
P,A	Sequences ID no.3,5 and 6 pages 91-93 claims	9-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 18771

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 17 (as far as the antagonists refers to an antibody of iL1 epsilon) and claims 18-20 are directed to a method of treatment of the human/animal body (rule 39.1 IV PCT), the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 7 partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17 partially

Claim 17 refers to a method of treatment involving an antagonist of iL-1epsilon without giving a true technical characterization. Moreover, no such compound is defined in the application. In consequence, the scope of said claim is ambiguous and vague, and its subject matter is not sufficiently disclosed and supported.
A partial search has been carried out for claim 17 as far as the antagonist relates to an antibody against iL-1epsilon as mentionned in claim 18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/18771

Patent document cited in search report	Publication date	Patent family member(s)	Publication dat
EP 0855404 A	29-07-1998	US 5863769 A JP 10304888 A	26-01-1999 17-11-1998
US 5449758 A	12-09-1995	NONE	
WO 9847921 A	29-10-1998	AU 7103198 A	13-11-1998